Do not adjust your mind – the fault is in your glia

Robin JM Franklin[1] and Edward T Bullmore[2,3]

[1]*Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute, Clifford Allbutt Building, Cambridge Biomedical Campus, University of Cambridge, Cambridge CB2 0AH, UK*
[2]*Department of Psychiatry, University of Cambridge, Cambridge, UK*
[3]*GlaxoSmithKline R&D, Stevenage, UK*

Glia have been implicated in schizophrenia, although whether they play a primary role is uncertain. In this issue, Windrem et al. (2017) transplant human glial progenitors from schizophrenia patients into mouse brains, which develop abnormalities and behaviors characteristic of schizophrenia, thereby suggesting glia's primary role in the complex disease pathogenesis.

Our understanding of the causes of schizophrenia, one of the most severe and widely occurring psychiatric disorders, has come a very long way from its characterization during most of the 20th century as a functional psychosis without an organic cause in terms of brain disorder. The biological basis of the disease in now beyond dispute, based on an ever increasing body of evidence from imaging, pathology and response to medication. However, at a cellular level, the mechanistic basis of the disease remains uncertain. In the study by Windrem and colleagues, the authors employ a highly imaginative stem-cell based approach to provide evidence for a primary role of glia, the non-neuronal cells of the CNS, in the aetiology of schizophrenia and in so doing, not only make a significant step forward in understanding the mechanistic basis of the disease, but also resolve a current 'chicken-and-egg' debate within the field.

The CNS comprises several types of cell. In addition to neurons, which, through their extensive network of processes and connections, establish the functional circuitry of the brain, there are two other major cell types - astrocytes and oligodendrocytes, the latter being the myelin-forming cells of the CNS. Collectively the astrocytes and oligodendrocytes are called glia – a term coined by Rudolf Virchow in the 19th century to describe the non-neuronal cells of the CNS. The term glia, derived from the Greek for glue, reflects the mystery that originally surrounded these cells – in the absence of any more informed understanding they were regarded as the cells that 'glued' the apparently more important neurons together. The historical uncertainty about what glia did led to a neuron-centric view of the CNS and its diseases. It is not surprising therefore that one of the earlier and now best established biological models of the underlying mechanisms of schizophrenia was based on a primary dysfunction in dopamine neurons (the dopamine hypothesis) (Howes and Kapur, 2009). However, in recent years, a primary pathogenic role for glia has emerged in several diseases which ultimately manifest themselves as neuronal disorders including some of the classic neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS – or motor neuron

disease) and Huntington's disease (Benraiss et al., 2016; Kang et al., 2013). There is even growing evidence for a role for glia in Alzheimer's disease. These discoveries are entirely consistent with the emergent recognition of a central trophic role for both astrocytes and myelinating oligodendrocytes in maintaining neuronal (and axonal) health and integrity (Nave, 2010). If glia play key roles in these diseases, then why not in a highly complex psychiatric disorder such as schizophrenia? Several lines of evidence have emerged over the last few years to indicate that astrocytes and oligodendrocytes are perhaps not passive bystanders. First, imaging studies have revealed a paucity of white matter (the main myelinated part of the CNS) in schizophrenics (McIntosh et al., 2008). Second, pathological studies suggest that schizophrenics have abnormal myelin (Uranova et al., 2011). Third, genetic studies have highlighted significant changes in expression of both astrocyte and oligodendrocyte associated genes (Hakak et al., 2001). However intriguing these data, do they point to a primary role for glia in the disease? The difficulty is that all of these changes could potentially be explained as secondary to a primary neuronal problem. For example, since many neurons project their axons through regions of white matter, then it is inevitable that there will be white matter changes if something goes awry with the neurons. The white matter changes *per se* do not provide compelling evidence for a causal role for glia.

To resolve the question of whether glia play a primary role in schizophrenia, Windrem and colleagues have adopted an ingenious experimental approach that represents one of the most creative and compelling uses of stem cell technology for disease modelling (Windrem el al., 2017). A number of years ago, while developing strategies for cell based therapies of myelin diseases, the laboratory of Steven Goldman (senior author in the paper by Windrem and colleagues) discovered that if human glial progenitor cells are grafted into the CNS of a new-born mouse, the human cells out-compete the endogenous mouse cells, resulting in a mouse developing with mouse neurons but human astrocytes, oligodendrocytes and glial progenitors (Windrem et al., 2014). Alert to the enormous potential of these mouse-human brain chimeras, the Goldman laboratory embarked on a series of studies that have transformed our understanding of glial cell biology, including the remarkable and previously under-recognised contribution that glia make to cognitive function (Han et al., 2013). Now the laboratory has used iPSC technology to generate glial progenitors from skin samples taken from individuals with schizophrenia as well as from non-psychotic control individuals. When these schizophrenia-derived glial progenitors are transplanted into new-born mice, the mice develop with normal mouse neurons surrounded by 'schizophrenic' glia, albeit with decreased myelination and abnormally shaped astrocytes. Although challenging to assess, a number of mouse behavioural tests can be used to measure phenotypes that are analogous to the cognitive and behavioural changes expected in patients with schizophrenia. When subjected to these tests, the mice with 'schizophrenic' glia revealed signs of having 'schizophrenic' behaviour. Thus, by an elegant experimental approach, the study provides unambiguous evidence that glia do indeed play a primary role in the disease pathogenesis, and that not all of the previously reported glial changes associated with the disease are

secondary consequences of primary neuronal pathology. This is not to say that there is not a primary neuronal component (which there almost certainly is), although a different approach is required to separate the neuronal from the glial component since the chimeric CNS model in which the species origin of the neurons and glia is reversed is not technically feasible.

While representing a significant step forward in our understanding of the cellular basis of schizophrenia, many intriguing questions still remain to be answered. For example, the present study does not distinguish between the relative contributions made between astrocytes, oligodendrocytes or indeed their progenitors. There is also a wealth of data that has been generated in the study comparing gene expression patterns of schizophrenic versus normal human glia. Separating signal from noise and identifying the key genes responsible for the disease phenotype will be a substantial task. Nevertheless, this challenging task will be worth embarking on since it is likely to lead to new and profound mechanistic insights into this complex disease with implications for innovative approaches to diagnosis, prediction and treatment of schizophrenia in the future.

Benraiss, A., Wang, S., Herrlinger, S., Li, X., Chandler-Militello, D., Mauceri, J., Burm, H.B., Toner, M., Osipovitch, M., Jim Xu, Q., Ding, F., Wang, F., Kang, N., Kang, J., Curtin, P.C., Brunner, D., Windrem, M.S., Munoz-Sanjuan, I., Nedergaard, M., Goldman, S.A., 2016. Human glia can both induce and rescue aspects of disease phenotype in Huntington disease. Nat Commun 7, 11758. doi:10.1038/ncomms11758

Hakak, Y., Walker, J.R., Li, C., Wong, W.H., Davis, K.L., Buxbaum, J.D., Haroutunian, V., Fienberg, A.A., 2001. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proc. Natl. Acad. Sci. U.S.A. 98, 4746–4751. doi:10.1073/pnas.081071198

Han, X., Chen, M., Wang, F., Windrem, M., Wang, S., Shanz, S., Xu, Q., Oberheim, N.A., Bekar, L., Betstadt, S., Silva, A.J., Takano, T., Goldman, S.A., Nedergaard, M., 2013. Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. Cell Stem Cell 12, 342–353. doi:10.1016/j.stem.2012.12.015

Howes, O.D., Kapur, S., 2009. The dopamine hypothesis of schizophrenia: version III--the final common pathway. Schizophr Bull 35, 549–562. doi:10.1093/schbul/sbp006

Kang, S.H., Li, Y., Fukaya, M., Lorenzini, I., Cleveland, D.W., Ostrow, L.W., Rothstein, J.D., Bergles, D.E., 2013. Degeneration and impaired regeneration of gray matter oligodendrocytes in amyotrophic lateral sclerosis. Nat. Neurosci. 16, 571–579. doi:10.1038/nn.3357

McIntosh, A.M., Muñoz Maniega, S., Lymer, G.K.S., McKirdy, J., Hall, J., Sussmann, J.E.D., Bastin, M.E., Clayden, J.D., Johnstone, E.C., Lawrie, S.M., 2008. White matter tractography in bipolar disorder and schizophrenia. Biol. Psychiatry 64, 1088–1092. doi:10.1016/j.biopsych.2008.07.026

Nave, K.-A., 2010. Myelination and the trophic support of long axons. Nat. Rev. Neurosci. 11, 275–283. doi:10.1038/nrn2797

Uranova, N.A., Vikhreva, O.V., Rachmanova, V.I., Orlovskaya, D.D., 2011. Ultrastructural alterations of myelinated fibers and oligodendrocytes in the prefrontal cortex in schizophrenia: a postmortem morphometric study. Schizophr Res Treatment 2011, 325789–13. doi:10.1155/2011/325789

Windrem, M.S., Osipovitch, M., Lui, Z., Bates, J., Chandler-Militello, D., Zou, L., Munir, J., Schanz, S., McCoy, K., Miller, R.H., Wang, S., Nedergaard, M., Findling, R.L., Tesar, P.J., Goldman, S.A., 2017 Human iPSC glial mouse chimeras reveal glial contributions to schizophrenia. Cell Stem Cell, xxxxxxxx

Windrem, M.S., Schanz, S.J., Morrow, C., Munir, J., Chandler-Militello, D., Wang, S., Goldman, S.A., 2014. A competitive advantage by neonatally engrafted human glial progenitors yields mice whose brains are chimeric for human glia. J. Neurosci. 34, 16153–16161. doi:10.1523/JNEUROSCI.1510-14.2014